

Indicators for the forecasting of malaria epidemics

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The entomological inoculation rate is presented as a comprehensive indicator of malaria transmission level, its relative changes reflecting the risk of potential epidemic development. This rate is a known function of several epidemiological direct factors and is particularly sensitive to the survival rate and the sporogonic cycle of the vector. Although not yet fully quantifiable, relationships exist between direct factors responsible for the transmission of infection and certain meteorological and environmental indirect factors like air temperature, relative humidity, or importation of malaria parasites.

The establishment of a two-stage monitoring system is suggested: the first stage would involve setting up a warning system based on the surveillance of the relevant indirect factors; at the appropriate time, this would trigger the second stage monitoring of the epidemiological direct factors having a definite bearing on the development of malaria outbreaks. It is recognized that the gain in reliability of the proposed approach depends largely on the progress still to be achieved in the quantification of the complex system of relations connecting the main direct factors with single or combined indirect factors. It is also noted that the proposed monitoring system should, in due course, provide the decision-makers with the epidemiological information required for the selection and implementation of intervention measures designed to prevent epidemic resurgences.

Prior to the launching of the WHO worldwide malaria eradication campaign, malaria epidemics were recurrent phenomena and the literature abounds with accounts of individual outbreaks. They varied in amplitude and periodicity and longer or shorter cycles have been recognized. Recently, several malaria epidemics have occurred in areas where the disease had been almost eliminated.

In the revised WHO strategy of the malaria eradication programme, it is recommended that control methods should be implemented according to the specific socioeconomic, epidemiological, and environmental conditions of the countries. Consequently, antimalaria measures should be concentrated in areas of socioeconomic importance and high malaria endemicity; their timing and coverage depend largely on the prevailing epidemiological trends. Early knowledge of natural events likely to trigger off epidemics would be of great assistance for the selection and timely application of preventive measures.

The purpose of this paper is to identify "indicators" for forecasting epidemic resurgences of malaria and to discuss their relative merits.

EPIDEMIOLOGICAL FACTORS

In the context of this paper, a malaria epidemic is defined as an exacerbation of the disease in an area where malaria was, or still is, usually of low or moderate endemicity. This occurs, in general, in areas where malaria is of the unstable type and subject to marked fluctuations. Areas of stable malaria, which are not subject to marked fluctuations over the years, are usually characterized by high collective immunity of the population and are unlikely to experience epidemics.

An epidemic cycle may be divided into 4: pre-epidemic, epidemic wave, post-epidemic and inter-epidemic.

Of particular interest is the pre-epidemic phase, that is, the "incubation period" during which the epidemic potential is building up. Either the local anopheline vectors are becoming more abundant or the number of gametocyte carriers is increasing. Sooner or later both events will be proceeding concurrently and create the epidemic wave. The basic interdependence of the human and anopheline factors explains the acceleration so characteristic of the later stages of the pre-epidemic period and of the ascending wave of a malaria epidemic (1).

Events that may precipitate epidemics are of various

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types: they act by altering directly or indirectly a pre-established equilibrium. For the sake of convenience they can be identified as direct and indirect factors.

Direct factors

These factors have a direct influence on the malaria transmission process; they can precipitate an epidemic by affecting any of the 3 living elements needed for the transmission cycle, namely, the mosquito, the parasite, and man. They are classified as:

1. Entomological factors

Changes in any epidemiological equilibrium can be expected or observed when one or more of the following entomological parameters is modified beyond certain limits:

- vector density in relation to man (m)
- daily survival rate of vector (p)
- man-biting frequency (a)
- length of the sporogonic cycle (n)
- proportion of anophelines with sporozoites that are actually infective (b).

2. Parasitological factors

The principal parasitological factors are:

- parasite rate (x)
- proportion of parasite carriers with gametocytes (g).

To allow the transmission cycle to take place, the reservoir of the infection must be available in the form of infective gametocytes. The species of the *Plasmodium* influences the timing of the outbreaks and the development of the epidemic curve: while *P. vivax* gametocytes appear practically at the same time as the asexual erythrocytic forms, those of *P. falciparum* appear 10–15 days after the occurrence of the initial parasitaemia. This, together with the difference in time of the extrinsic cycle, is responsible for the interval between generations of cases from gametocyte to gametocyte. In areas where the two *Plasmodium* species coexist, there are usually two epidemic waves, the first one due to *P. vivax* and the second to *P. falciparum* (2).

3. Immunological factors

The degree of human immunity plays a large role in the occurrence and severity of malaria epidemics. A low immune status of the community can favour the resurgence of a malaria epidemic, whilst the immunity produced by epidemics may partially suppress transmission or even bring it to an end (3).

Indirect factors

By intervening singly or in combination, these factors can create the conditions for an increased malaria transmission potential. Two main factors, meteorological and environmental, can be considered.

1. Meteorological factors

The climatic events that may modify and influence any of the entomological direct factors involved in the transmission cycle are:

(a) *Rainfall.* The influence of rainfall on breeding habitats is well known. Malaria epidemics were recorded in northern Sind, India, in years of unusually heavy rainfall, in combination with high flood levels in the river Indus (4). In 1934, the severe epidemic that occurred in Sri Lanka was related to the proliferation of breeding places attributable largely to drought and the pooling of rivers (5).

Heavy snowfalls in the Hindu Kush range of Afghanistan are responsible for a delayed start of transmission, and the low water temperature of the rivers in early spring is unfavourable for larval development. Later on, the abundance of water resulting from melting snow facilitates the wide proliferation of breeding places (Onori, personal observation).

(b) *Temperature and relative humidity.* In the Punjab, epidemics have been associated with a relatively high degree of humidity prevailing during the pre-epidemic period (6, 7). Knowles & Senior White (8) noted that in India, malaria transmission does not commence until a very high degree of humidity has been reached. In northern Sind excessive monsoon rainfall and the resulting lengthening of the period of high, sustained relative humidity were recognized as the main factors in the production of an epidemic (9). In southern China, an average relative humidity of 70–80%, together with a temperature between 18°C and 28°C, represented optimum conditions for malaria transmission (10).

The effect of increased humidity on mosquito longevity appears to be a prominent cause of many outbreaks, e.g., a dramatic epidemic in Maracaibo, Venezuela (11) and epidemics in Argentina (12).

Undue prolongation of the season favourable for transmission, e.g., warm weather for longer periods than usual, was recognized as the cause of the epidemics that occasionally occurred in Morocco (13) and the inland areas of South America (14).

2. Environmental factors

The main environmental factors can be classified as follows:

(a) *Increased anophelism due to human activities.* Abnormal increases in anopheline populations and the establishment of vectors outside their zone of distribution can be due to natural factors but are often due also to human activity (man-made malaria).

Examples of man-made malaria are the epidemics following canal constructions in India (15) including the Canvey Canal (16) and the Sind irrigation scheme

(9). Recently, an epidemic started in Adana Province in Turkey, where the local vector *Anopheles sacharovi*, which was multiresistant to insecticides of common use, found optimum breeding conditions in drainage canals resulting from the construction of the Seyham dam. Incorrect maintenance of the irrigation system and the creation of myriads of waste water collections were responsible for the proliferation of *A. sacharovi* (17).

In the North Eastern Region of Afghanistan, after the introduction of DDT house spraying and changes in the environment, *A. pulcherrimus* and *A. hyrcanus* replaced *A. superpictus* (18). These vectors found optimum conditions in breeding places created by the large extension of land under rice cultivation.

Multiplication of *A. fluviatilis* and *A. minimus* in India and *A. maculatus* in Malaysia was greatly enhanced by the large-scale clearing of the jungle and consequent exposure of breeding places to sunlight. In the Americas, lakeside breeding places of *A. quadrimaculatus* were provided by the construction of dams, and *A. darlingi* found ideal breeding sites along newly constructed irrigation canals (19).

(b) *Changes in feeding habits of mosquitos.* A zoophilic mosquito can become anthropophilic if suddenly deprived of its usual source of food. Deviation to man may be due to: (i) reduction in the number of cattle (e.g., following a war) as described in Okinawa (20) and in Italy (21), or (ii) invasion of towns by normally zoophilic anophelines. Such a change in feeding habits was fully documented in New Delhi (22) in connexion with the spread of *A. culicifacies* and a similar event was described in Indochina affecting *A. hyrcanus sinensis* (23).

(c) *Importation of malaria parasites.* The introduction of a reservoir of malaria parasites infective for the local anopheline fauna, especially in areas freed from the disease, is an important factor to be taken into account (e.g., in Sri Lanka, 1967–68, and in Turkey, 1970).

(d) *Migration of nonimmune people.* In areas where transmission is contained by natural resistance to the disease, the equilibrium may be upset by the dilution of this resistance, owing to the introduction of nonimmune persons. War and postwar epidemics may be attributable to such migrations which are often accompanied by physical disturbances inducing proliferation of anophelines. The 1939–43 outbreaks in Spain (24) and those reported from Italy after the Second World War (25–27) were caused in this way.

Epidemics associated with the assembling of large labour forces for major engineering works are a recurrent phenomenon.

SELECTION OF PARAMETERS FOR EPIDEMIC WARNING SYSTEMS

In the study of communicable disease dynamics, it has been found advantageous to express the level of incidence in terms of a comprehensive parameter called “force of infection”, which represents the total impact of all the factors involved in the transmission of infection (28).

As far as malaria transmission is concerned, the force of infection is usually measured by the parasitological inoculation rate, h . This rate, defined as the mean daily number of bites inflicted on one individual by mosquitos whose salivary glands contain sporozoites that are actually infective, takes the algebraic form:

$$h = mabs \quad (1)$$

where ma is the daily man-biting rate, b the proportion of anophelines with sporozoites that are actually infective, and s the sporozoite rate.

Taking into account the mathematical expression of the sporozoite rate (19) one can write:

$$h = \frac{ma^2 b g x p^n}{agx - \log_e p} \quad (2)$$

This equation shows that the parasitological inoculation rate results from a combination of all the entomological and parasitological direct factors referred to above. They are all measurable by field and laboratory observations, except the factor b , the proportion of anophelines with sporozoites that are actually infective. This factor, however, is affected little, if at all, by changes in the indirect factors, at least so long as the immunity level has not been substantially modified in the population.

For the present purpose it would, therefore, be convenient to refer to the entomological inoculation rate, h' defined by the equation (29):

$$h' = h/b \quad (3)$$

or

$$h' = \frac{ma^2 g x p^n}{agx - \log_e p} \quad (4)$$

after replacing h by its expression given in equation (2).

Furthermore, the feeding habit of the vector on man, a , can be considered as constant for a given mosquito species and for a limited period of time;^a it is made equal to one-third in the examples presented below. Hence equation (4) becomes:

$$h' = \frac{ma g x p^n}{gx - 3 \log_e p} \quad (5)$$

^a Sudden changes in the value of a are unlikely except after events modifying the relationship between man and mosquito, e.g., changes in cattle population or drastic changes in the human ecology.

From this equation it is clearly seen that changes in the entomological inoculation rate, h' , will result from any modification in at least one of the following 4 individual or combined direct factors:

- the daily man-biting rate, ma
- the daily survival rate of vector(s), p
- the length of the sporogonic cycle in days, n
- the rate of gametocyte carriers, gx .

In order to appreciate the risk of epidemic development, it would be useful to know the quantitative impact on the inoculation rate of common changes in these basic parameters.

A simplified approach is illustrated by the numerical examples presented in Table 1, where the value of the entomological inoculation rate has been calculated successively for 5 different levels of each parameter in turn, keeping the 3 others constant at their medium value.

As already stated, the epidemiological situation of relevance to the present problem is characterized by a low or very low level of endemicity. Therefore, over the 5 situations illustrated, the range of variation envisaged for the entomological inoculation rate was kept within the limits actually observed when the transmission level is low: its value is about 0.001 for the first situation and about 0.050 for the fifth situation; such values of the entomological inoculation rate correspond to 1 infected (but not necessarily effective) contact in 1000 days and 1 in 20 days, respectively.

It should be noted that the 5 situations listed are, in each case, independent and do not reflect the actual dynamic changes in the inoculation rate, as the above-mentioned basic parameters are mutually related. For instance, it is evident that a change in the man-biting

rate, ma , will quickly result in a modification of the parasite rate, x , in the population. Keeping this in mind, it can be seen from Table 1 (columns 1–6) that, as it should be, the inoculation rate is proportional to the man-biting rate, ma , and because of the low levels of parasite rate considered here, a similar proportionality is observed for the gametocyte rate, gx . The situation is quite different with regard to the other 2 parameters: a reduction by half in the sporogonic cycle (n) corresponds to a tenfold increase in the inoculation rate (Table 1, columns 7–9), and, for each increase of 5% in the survival rate of the vector (p), the inoculation rate increases almost 3 times (Table 1, columns 10–12).

An attempt to evaluate the relative sensitivity of the inoculation rate to the basic individual or combined direct factors is summarized in Table 2. The scale of the inoculation rate has been fixed so that its value doubles in each successive situation, covering the range from 0.0016 to 0.0256, considered representative of the epidemiological pattern concerned (see column 1). The rest of the table shows independently for each of the 4 parameters the actual values required to observe the inoculation rates in column 1, assuming that in each case the other 3 parameters remain at the level fixed for the medium situation (line 3). For instance, it can be seen that when the gametocyte rate (column 5), the sporogonic cycle (column 7), and the vector survival rate (column 9) are all kept at their medium value (respectively 0.030, 12.0 and 0.750), a decrease by half of the man-biting rate (from 6.0 to 3.0 in column 3) will result in a reduction in the entomological inoculation rate of the same magnitude (50.0%), that is from 0.0064 to 0.0032 (column 1). On

Table 1. Comparative levels of the entomological inoculation rate for situations differing by the value of a single parameter only^a

Situation	Entomological inoculation rate			Entomological inoculation rate			Entomological inoculation rate			Entomological inoculation rate		
	Values of ma (1)	Actual value (2)	Relative change (3)	Values of gx (4)	Actual value (5)	Relative change (6)	Values of n (7)	Actual value (8)	Relative change (9)	Values of p (10)	Actual value (11)	Relative change (12)
1	2	0.0021	100	0.01	0.0022	100	16	0.0020	100	0.65	0.0008	100
2	4	0.0043	205	0.02	0.0043	195	14	0.0036	180	0.70	0.0023	288
3	6	0.0064	305	0.03	0.0064	291	12	0.0064	320	0.75	0.0064	800
4	8	0.0085	405	0.04	0.0084	382	10	0.0114	570	0.80	0.0177	2213
5	10	0.0106	505	0.05	0.0104	473	8	0.0202	1010	0.85	0.0495	6188

^a For any given parameter the values of the other 3 parameters are those printed in italics and corresponding to the medium situation (3).

Table 2. Comparative values of individual parameters^a corresponding to a fixed scale of inoculation rate levels

Situation	Entomological inoculation rate		Man-biting rate <i>ma</i>		Gametocyte rate <i>gx</i>		Sporogonic cycle <i>n</i>		Vector survival rate <i>p</i>	
	Actual value (1)	Relative change (2)	Actual value (3)	Relative change (4)	Actual value (5)	Relative change (6)	Actual value (7)	Relative change (8)	Actual value (9)	Relative change (10)
1	0.0016	25	1.5	25	0.0073	24	16.8	140	0.684	91
2	0.0032	50	3.0	50	0.015	50	14.4	120	0.717	96
3	0.0064	100	<i>6.0</i>	100	<i>0.030</i>	100	<i>12.0</i>	100	<i>0.750</i>	100
4	0.0128	200	12.0	200	0.062	207	9.6	80	0.784	105
5	0.0256	400	24.0	400	0.134	447	7.2	60	0.818	109

^a For any given situation, the values of the other 3 parameters are those printed in italics and corresponding to the medium situation (3).

the other hand, the same 50% decrease in the entomological inoculation rate from its medium value can be obtained by a 4% reduction in the vector survival rate (from 0.750 to 0.717 in column 9), while the other 3 parameters retain their medium value.

The conclusion that can be drawn from Table 2 is that, adopting the schematic and simplified approach presented here, a 16-fold increase in the inoculation rate could be brought about in any of the following ways: (a) if the man-biting rate reveals an increase of the same order; (b) if the gametocyte rate increases about 18 times; (c) if the sporogonic cycle decreases by less than 60%; or (d) if the vector survival rate increases by not more than 20%. The table confirms that the inoculation rate is extremely sensitive to slight changes in the last two biological parameters of the vector—its survival rate and the sporogonic cycle—which would therefore require special attention.

Table 3. Direct factors and main indirect factors influencing them

Direct factors	Indirect factors with the greatest impact
Man-biting rate (<i>ma</i>)	Rainfall, drought, incorrect maintenance of irrigation systems, and changes in feeding habits of mosquitos
Rate of gametocyte carriers (<i>gx</i>)	Importation of malaria parasites, and migration of non-immune people
Length of sporogonic cycle (<i>n</i>)	Air temperature
Daily survival rate of vector(s) (<i>p</i>)	Air temperature and relative humidity

As already indicated, all the direct factors discussed above are affected by modifications in certain indirect factors. The careful monitoring of properly selected indirect factors could therefore be considered a powerful approach for forecasting the potential development of malaria epidemics.

In Table 3 the direct factors are listed in the order of increasing sensitivity to the entomological inoculation rate, together with the corresponding most important indirect factors amongst those that have an influence on them.

It has already been mentioned that heavy rainfall or prolonged periods of drought, incorrect maintenance of irrigation systems, and changes in agricultural practices can promote the proliferation of breeding places and therefore increase the mosquito densities in relation to man; such an increase can also be brought about by changes in the feeding habits of vectors. It is also obvious that importation of malaria parasites into a malaria-free area or the arrival of nonimmune persons in malarious areas affects the parasite reservoir.

Changes in temperature affect the length of the sporogonic cycle, while changes in temperature and relative humidity have an impact on the daily survival rate of mosquitos (30). Usually, longevity increases directly with relative humidity and inversely with temperature until a lethal point is reached (31–33). The impact of these atmospheric parameters on the vector biology may vary under different local conditions; to improve our knowledge, it is suggested that longitudinal studies be carried out to elucidate further the functional relationship between the indirect and direct factors.

Of course, two or more variables may change simultaneously (e.g., heavy rainfall may coincide with increase of temperature and relative humidity), with the result that mosquito densities, the survival rate of

the mosquitos, and the length of the sporogonic cycle are all affected at the same time.

Precise knowledge of the relationships existing between indirect and direct factors would evidently be of considerable interest for forecasting the epidemiological developments that might be expected from modifications detected in the indirect factors through an adequate monitoring system.

Simple mathematical formulations have already been established for expressing some direct factors in terms of indirect factors. For instance, Oganov (34) has determined the length of the sporogonic cycle as a function of the mean air temperature. In other cases, an important direct factor can itself be a function of another direct factor, as for example the daily survival rate of the vector, usually calculated from the parity rate and feeding rhythm peculiar to the biting mosquitos (35).

In the majority of cases, the situation unfortunately looks too complex to permit a satisfactory quantification of the relations between the main direct factors and various independent or combined indirect factors, although some future progress in this direction should not be considered as completely unrealistic. The promising potentiality of new mathematical modelling approaches and computerized simulation techniques, with particular reference to their application to the epidemiology and control of malaria, has been discussed by Bailey (36). A model usable as a tool for the planning of malaria control has been constructed by Dietz et al. (37) and actually tested in the African savanna. The ability of the model to simulate the epidemiology of *P. falciparum* under different conditions was further tested by Molineaux et al. (38).

Except in a few instances, quantitative changes in direct factors and precise estimates of critical levels cannot be derived, at present, from observed values of the indirect factors that influence them. Therefore, permanent surveillance and recording of such indirect factors would constitute only a warning system, which at the appropriate time, would trigger the monitoring of the above-mentioned direct factors that have a recognized bearing on the possible development of malaria outbreaks and that, as already mentioned, can be measured directly in the field.

DISCUSSION AND CONCLUSION

One of the most comprehensive indicators of the level of malaria transmission is the entomological inoculation rate, relative changes in which seem able to provide an indication of the risk of epidemic development. In principle, this rate could easily be measured, since it is directly proportional to the man-biting, ma , and the sporozoite rate, s (see equations (1)

and (3)). When, however, the level of transmission is not high, the sporozoite rate is usually rather low. For instance, when the parametric values are those characterizing the medium situation in Tables 1 and 2, the corresponding sporozoite rate is 0.10%; its confidence interval at the 95% probability level varies according to the number of mosquitos dissected as shown below:

Sample size	95% confidence interval (%)
2 000	0.01–0.36
4 000	0.02–0.26
8 000	0.04–0.20

In other words, if a sporozoite rate of 0.10% is observed after dissecting as many as 8000 mosquitos, the true rate could still be less than half (0.04%), or twice (0.20%) this value.

As established by Macdonald (19), the sporozoite rate is a function of the 3 main direct factors: the vector survival rate, the sporogonic cycle, and the gametocyte rate. Therefore, the inoculation rate can also be calculated without estimating the sporozoite rate directly (see equation (2)).

Information presented in Table 2 clearly demonstrates the relatively higher sensitivity of the inoculation rate to the length of the sporogonic cycle, n and to the daily survival rate of the vector, p .

It has also been noted that while some indirect factors like air temperature and humidity are liable to affect the sporogonic cycle and the daily survival rate of the vector, others, such as rainfall or importation of malaria parasites, affect the biting-rate and the rate of gametocyte carriers. Consequently, continuous observation of the indirect factors, and more especially of those affecting the survival rate of vectors and the length of the sporogonic cycle, should be considered as the most useful surveillance procedure for detecting changes in the value of the epidemiological variables having a bearing on the transmission process.

Whenever there are changes in one or more indirect factors, a monitoring system should be established by which the epidemiological variables affected by the indirect factors can be calculated frequently at regular intervals and their values analysed and assessed with the shortest possible delay. The time intervals between the observations may vary according to different epidemiological situations and it is for the epidemiologist to decide when they should be repeated. Observations at 15-day intervals during the period of expected changes in the entomological inoculation rate seem to be reasonable in countries of unstable malaria where epidemics have occurred or are likely to occur and where indirect factors are known to create concomitantly or in isolation favourable conditions for an increased malaria transmission.

The establishment of the proposed two-stage monitoring system should be based on sound principles. Due consideration should be given to the statistical procedures relating to the collection, recording, and processing of the data. Good monitoring will also involve various statistical methods, such as sampling techniques and decision theory. The main statistical requirements of monitoring and surveillance systems have been discussed by a WHO meeting (39).

The comprehensive monitoring system needs adequate adaptation to both the environmental and the epidemiological profiles specific to the area concerned, as the first stage would require a warning system based on the surveillance of indirect factors,

while the second stage would be concerned with the monitoring of the epidemiological variables (direct factors), when required.

The second stage monitoring system described in this paper has another practical and very important advantage. As variations in the epidemiological profile of a situation depend upon the changing value of a number of direct factors having a bearing on the transmission potential, the timely observations of those factors may assist: (a) in deciding when and where it is necessary to intervene, and (b) in selecting the most appropriate intervention measures. Information on both direct and indirect factors will also help in planning the most efficient programme of application.

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RÉSUMÉ

INDICATEURS POUR LA PRÉVISION DES ÉPIDÉMIES DE PALUDISME

Le taux d'inoculation entomologique, défini dans l'article ci-dessus, constitue un indicateur très sensible du niveau de transmission du paludisme car il tient compte de l'ensemble des facteurs influant sur cette transmission, et toute modification de ce taux reflétant une variation intervenue dans l'un ou l'autre des paramètres qui permettent de le calculer peut faire craindre l'apparition d'une épidémie. Parmi les divers paramètres épidémiologiques en fonction desquels le taux d'inoculation entomologique varie selon une équation mathématique, les plus importants sont le taux de survie du vecteur et son cycle sporogonique. En outre, et bien que celui-ci ne soit pas complètement quantifiable, il existe un rapport bien établi entre les facteurs directement associés à la transmission de l'infection et certains facteurs météorologiques et environnementaux comme la température de l'air, l'humidité ou l'importation de parasites du paludisme.

La mise sur pied d'un système de surveillance comportant

deux étapes est suggérée. Dans un premier temps, on constituerait un système d'alarme fondé sur la surveillance des facteurs indirects entrant en ligne de compte; ceci permettrait de déclencher au moment approprié la mise en route de la deuxième étape, soit le contrôle des facteurs épidémiologiques ayant une influence directe sur l'apparition des épidémies de paludisme. Il va sans dire que cette approche sera d'autant plus fiable que des progrès auront été enregistrés dans la quantification du système complexe de relations existant entre les principaux facteurs directs et les facteurs indirects considérés isolément ou en combinaison. Ceci étant, le système de surveillance proposé devrait, le moment venu, fournir aux administrateurs de la santé publique les renseignements épidémiologiques permettant le choix et l'exécution des mesures appropriées pour prévenir la réapparition de poussées épidémiques de paludisme.

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